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Factors determining renal response to water immersion in non-excretor cirrhotic patients

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Factors determining renal response to water immersion in non-excretor cirrhotic patients. Non-excretor cirrhotic patients, defined by their inability to normally excrete a standard water load, display variable responses to head–out water immersion. The hemodynamic, hormonal, and renal functional status of fifteen such patients were analyzed relative to water excretion during head–out water immersion. Group 1 patients ($N = 7$) all excreted less than 40% of the water load during immersion, whereas excretion was greater than 40% in all eight patients in Group 2. Group 1 patients, when compared with Group 2, had more ascites, more diuretic resistance, lower serum sodium concentration (125 ± 2 vs. 130 ± 1 mEq/liter, $P < 0.05$), and more impaired baseline water excretion (12.9 ± 1.2 vs. 35.9 ± 5.9% of water load in 5 hr, $P < 0.005$). Systemic hemodynamic responses to water immersion were similar in both groups. Glomerular filtration rate and renal plasma flow were significantly more impaired in Group 1 patients (inulin clearance 28 ± 6 vs. 62 ± 9 ml/min/1.73 m^2, $P < 0.05$; para-aminohippurate clearance 212 ± 35 vs. 357 ± 37 ml/min, $P < 0.05$). Concentrations of plasma vasopressin (1.7 ± 0.5 vs. 0.8 ± 0.1 pg/ml, $P < 0.05$), renin (8.6 ± 1.7 vs. 3.8 ± 0.9 ng/ml/hr, $P < 0.05$), aldosterone (82 ± 14 vs. 39 ± 10 ng/dl, $P < 0.05$) and norepinephrine (1155 ± 183 vs. 603 ± 126 pg/ml, $P < 0.05$) were all significantly higher in Group 1 than Group 2 patients during water immersion. Thus, non-excretor cirrhotic patients are not homogenous and appear to comprise a spectrum with those patients in whom water excretion is most impaired, having tense ascites, diuretic resistance, lower serum sodium concentrations, more impaired renal function, and more marked abnormalities in the hormonal markers of decreased effective blood volume.

Patients with cirrhosis have been shown to have impaired sodium and water excretion [1–4], but this abnormality has not been consistent [3, 4]. In a recent study, cirrhotic patients were reported to be divisible into those who excreted a standard intravenous 20 ml/kg water load normally (excretors) and abnormally (non-excretors) [1]. The results of these studies demonstrated that the non-excretor patients exhibited hormonal characteristics compatible with diminished effective blood volume, including a significantly higher plasma renin, aldosterone, norepinephrine and vasopressin concentrations than the excretor patients [1]. The non-excretor patients also exhibited more sodium retention, ascites, hyponatremia and hypoalbuminemia. Head–out water immersion improved renal sodium and water excretion in these non-excretor patients [5, 6].

The purpose of the present study was to investigate further the nature of the impaired water excretion in non-excretor patients. In the present study, the hypothesis was further examined that cirrhosis is associated with a continuum of diminished effective blood volume and impaired water excretion, which can be demonstrated beyond that described in the previous study of excretor and non-excretor patients [1]. Specifically, the reasons for the often variable responses of cirrhotic patients to central blood volume expansion with head–out water immersion have not been fully elucidated [3]. Fifteen non-excretor patients (<80% of an intravenous water load excreted) were, therefore, studied in a prospective manner to examine whether hormonal indices of a diminished effective blood volume were significantly different in cirrhotic non-excretor patients who, during immersion, excreted less than 40% of a water load versus those who excreted greater than 40% of a water load during immersion. This should be the case if the response to an acute water load is an index of effective blood volume in cirrhotic patients.

Methods

Fifteen patients (12 males and three females), aged 31 to 63 years, were admitted to the Clinical Research Center of the University of Colorado Health Sciences Center. All had alcoholic cirrhosis except for one woman in whom cirrhosis was secondary to hepatitis B infection, and all manifested some degree of ascites (that is, decompensation). Medications were discontinued at least five days prior to study, and patients ingested a 40 mEq sodium diet daily. Fluid intake was restricted only if the plasma sodium concentration was below 125 mEq/liter. Informed consent was obtained and the protocol was approved by the Human Subjects Committee. This study was comprised of two phases in each patient; these phases were performed in random order.

Phase 1: Water load

Patients were awakened at 7:00 a.m. to void spontaneously. They remained semi-recumbent for the duration of the test, except when standing to void at hourly intervals. Intravenous cannulae were placed in each forearm and loading doses of para-aminohippuric acid (PAH, 0.08 mg/kg i.v.) and inulin (60 mg/kg i.v.) were then followed by a continuous intravenous

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infusion (30 ml/hr) of 5% dextrose solution containing inulin (60 mg/ml) and PAH (0.08 mg/ml).

After 10 min of this sustaining infusion, the water load was administered intravenously over 30 to 40 min as 20 ml/kg D_5W. Hourly blood samples were taken from the contralateral forearm for estimations of plasma sodium, osmolality, creatinine, inulin, PAH, renin, aldosterone, norepinephrine, and vasopressin. Hourly urine samples, always obtained after the corresponding blood samples, were analyzed for sodium, osmolality, inulin, PAH (17), and creatinine. Blood pressure was measured hourly, using an arm cuff. The test was terminated 5 hr after infusion of the water load. The results are expressed as the percent water load excreted over 5 hr.

Phase 2: Water load during head–out water immersion

In this phase, the water loading procedure as described in Phase 1 was repeated during head–out water immersion in a temperature controlled steel tank at 35.5°C with the patient in a semi-recumbent position, as previously described [5, 6]. In 11 of the 15 patients, a Swan–Ganz catheter was placed via percutaneous puncture of the basilic vein in the antecubital fossa for measurements of right atrial (RAP), pulmonary artery (PAP), and pulmonary wedge (PWP) pressures. Four patients were studied in Group 1 and seven patients in Group 2. Pressure recordings utilized a Gould–Statham P231d transducer and an Electronic for Medicine VR6 Photographic recorder (White Plains, New York, USA). Cardiac output (CO) was measured using the thermodilution technique and a Model 9520 Edwards Laboratories computer. Values for mean arterial pressure (MAP), cardiac index (CI), and systemic vascular resistance (SVR) were calculated by the standard formulae:

MAP (mm Hg) = 1/3 (systolic BP + 2 diastolic BP);

CI (liter/min/m^2) = cardiac output (CO)/body surface area;

SVR (dynes · sec · cm^{-5}) = 80 (MAP-RAP)/CO.

Pre-immersion measurements of CO, MAP, RAP, PAP, PWP, and SVR were obtained in the semi-recumbent position and repeated hourly during water immersion. All catheters were removed at the end of the 5 hr test.

Biochemical measurements and determinations of renin, aldosterone, norepinephrine and vasopressin were performed using the standard techniques previously described in this laboratory [6]. Values reported for each hormone are the mean of 5 hourly determinations during each water load.

On the basis of the percentage of water load excreted during Phase 2, the patients were divided into two groups: Group 1, $N = 7$, who excreted less than 40% of the administered water load during 5 hr of immersion and Group 2, $N = 8$, who excreted more than 40% of the water load during immersion (Fig. 1).

Prior to study, all patients had been hospitalized for treatment of ascites with bed rest and diuretics. Daily weights and abdominal girths were available over seven to 14 days in all patients; the patients were on similar diuretic regimens (Table 1), salt intakes (40 to 50 mEq/day) and bed rest regimens. The ascites was graded in each patient on a 1 to 4 scale with 4+ indicating the most tense ascites.

Statistical analysis utilized paired or unpaired *t*-tests, as appropriate. Results are given as mean ± standard error of the mean (SEM). A P value less than 0.05 was considered statistically significant.

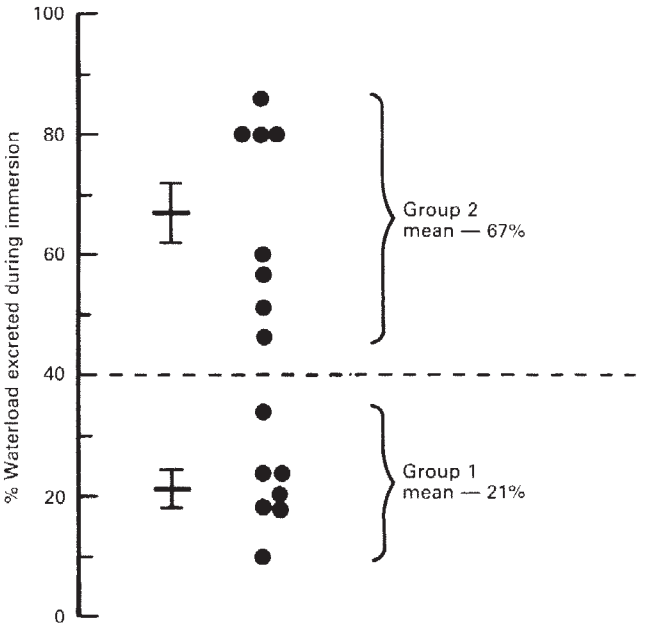

Fig. 1. *Water load excretion during immersion.* Patients were subdivided into Group 1 (<40% excretion) and Group 2 (>40% excretion). The patients in both groups were non-excretor before immersion since all excreted less than 80% of the water load. However, as noted in Figure 4, four patients excreted 80% or greater of the water load during immersion.

Table 1. Clinical features

	Group 1	Group 2
Age, *years*	55.1 ± 3.6	46.3 ± 3.1
Sex	2F, 5M	1F, 7M
Pulse	92 ± 4	84 ± 3
Systolic BP, *mm Hg*	111 ± 6	112 ± 4
Diastolic BP, *mm Hg*	74 ± 3	69 ± 3
Plasma albumin, *g/dl*	2.5 ± 0.2	2.8 ± 0.2
Tense ascites, *4+*	7/7	1/8

Table 2. Diuretic responsiveness to identical regimens of bed rest, sodium restriction, and furosemide and spironolactone

	Group 1	Group 2	*P* value
Weight loss, *kg/day*	0.13 ± 0.09	0.54 ± 0.16	<0.05
Abdominal girth decrease, *cm/day*	0 ± 0.1	1.0 ± 0.3	<0.05
Daily dose, *mg*			
Furosemide	68 ± 32	67 ± 59	NS
Spironolactone	254 ± 37	221 ± 53	NS

Results

Clinical features

The major pertinent clinical features of the patients are summarized in Table 2. The slightly older age and higher pulse rates in Group 1 patients were not statistically significant. Tense ascites (4+) was a constant feature of the patients in Group 1, whereas it was present in only one of the eight patients in Group 2.

Table 3. Hemodynamic changes between control and immersion in Group 1 and Group 2 cirrhotic patients[a]

	Group 1			Group 2*		
	Control	Immersion	*P* value	Control	Immersion	*P* value
PWP	11.8	16.1		8.1	14.9	
mm Hg	±3.0	±2.5	<0.01	±1.5	±1.5	<0.005
CI	3.78	4.7		4.2	5.1	
liter/min/m²	±0.9	±1.2	<0.05	±0.4	±0.5	<0.005
SVR	973	750		921	692	
dynes · sec · cm^{-5}	±217	±304	<0.05	±114	±94	<0.05
MAP	86	83		83	81	
mm Hg	±3	±3	NS	±3	±1	NS

[a] Abbreviations are: PWP, pulmonary wedge pressure; CI, cardiac index; SVR, systemic vascular resistance; MAP, mean arterial pressure. Symbol is: * None of the changes from control to immersion in Group 1 were significantly different from the changes in Group 2.

In Table 1 are shown the diuretic responsiveness in both patient groups. The doses of diuretic drugs were almost identical in both groups, but the response as assessed by weight loss and decrease in abdominal girth was much less in patients in Group 1.

Laboratory data

Baseline serum sodium concentrations were significantly lower in patients in Group 1 than Group 2 (125 ± 2 vs. 130 ± 1 mEq/liter, $P < 0.05$). Before immersion, water excretion was also much lower in Group 1 than Group 2 patients (12.9 ± 1.2 vs. 35.9 ± 5.9% over 5 hr, $P < 0.005$).

The effects of immersion on systemic hemodynamics in both groups are shown in Table 3. As previously described [5, 6], CI and PWP increased, SVR decreased and MAP was unaltered during the maneuver. These control values and the value during immersion were not significantly different between Group 1 and Group 2 (Table 3). During control water loading, mean urinary sodium excretion ($U_{Na}V$) was 4.5 ± 1.3 μEq/min in Group 1 and 10.9 ± 3.5 μEq/min in Group 2 (NS). During immersion, however, Group 2 patients significantly increased $U_{Na}V$ (to 25.6 ± 6.8 μEq/min, $P < 0.02$) whereas Group 1 patients did not (to 12.6 ± 5.8, NS).

Inulin clearance, corrected for body surface area, was significantly lower in Group 1 than Group 2 patients, both during control (28.3 ± 6.1 vs. 62.1 ± 8.6 ml/min/1.73 m^2, $P < 0.05$) and immersion (34.1 ± 7.8 vs. 79.6 ± 13.5 ml/min/1.73 m^2, $P < 0.05$) (Fig. 2). Simultaneous creatinine clearances demonstrated the same changes during control (54.5 ± 10.6 vs. 81.0 ± 9.2 ml/min, $P < 0.05$) and immersion (63.9 ± 10.4 vs. 98.4 ± 11.8 ml/min, $P < 0.05$). The increase in inulin clearance with immersion was statistically significant only in Group 2 ($P < 0.05$). Para-aminohippurate clearances were also lower in Group 1 than Group 2, both during control (212 ± 35 vs. 357 ± 37 ml/min, $P < 0.02$) and immersion studies (247 ± 40 vs. 399 ± 48 ml/min, $P < 0.05$) (Fig. 2). The renal vascular resistances were lower in Group 2 than Group 1 patients during control (0.541 ± 0.097 vs. 0.353 ± 0.064) and immersion (0.246 ± 0.026 vs. 0.225 ± 0.038), but these decreases were not statistically significant.

Control plasma vasopressin concentrations were significantly higher in Group 1 than Group 2 (2.3 ± 0.5 vs. 1.0 ± 0.2 pg/ml, $P < 0.05$). During water immersion, vasopressin was also higher in Group 1 patients (1.7 ± 0.5 vs. 0.8 ± 01, $P < 0.05$) (Fig. 3), and suppressed significantly during immersion only in Group 2 patients ($P < 0.02$). Normal values for vasopressin in a water–loaded subject are below the threshold sensitivity of the assay (<0.5 pg/ml).

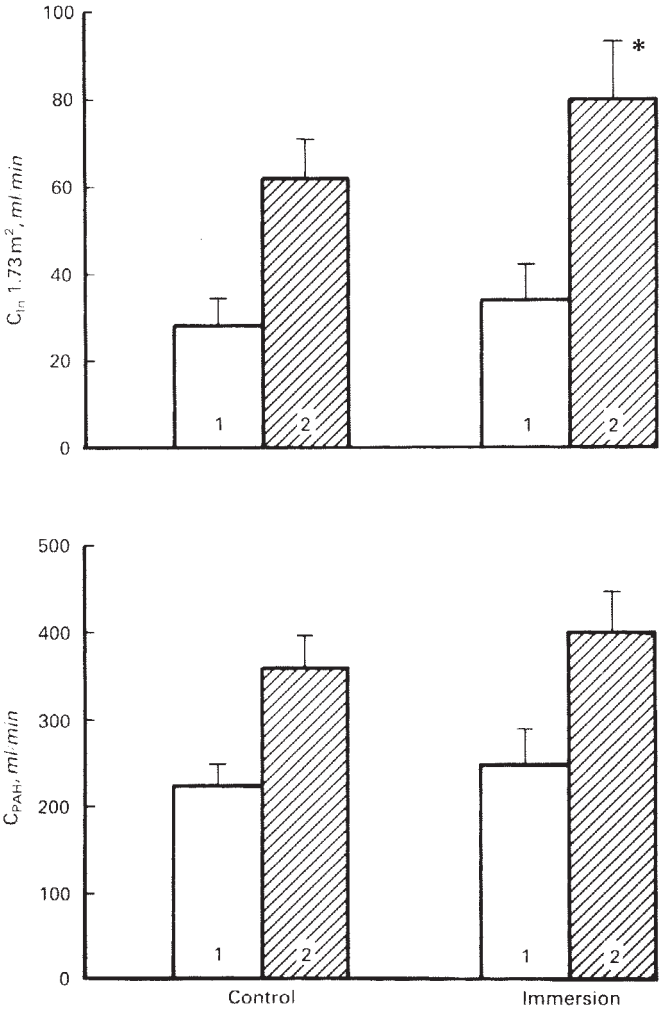

Fig. 2. *Inulin (C_{In}) and para-aminohippurate (PAH) clearances are lower in Group 1 than Group 2 decompensated cirrhotic patients, both during control and immersion.* Group 2 patient's C_{In} was significantly higher ($P < 0.05$) during immersion than control.

Control plasma renin activity was also significantly higher in Group 1 patients as compared with Group 2 (11.6 ± 2.5 vs. 4.9

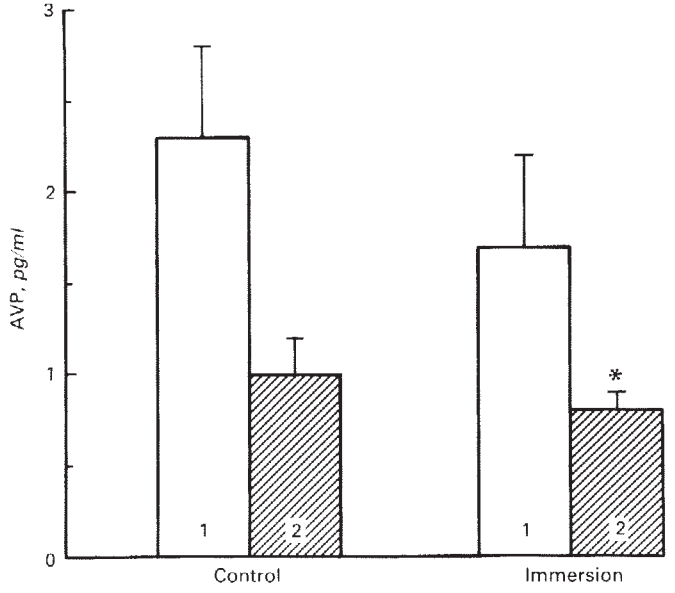

Fig. 3. *Plasma arginine vasopressin (AVP) levels are higher in Group 1 than Group 2 decompensated cirrhotic patients, both during control and immersion.* The AVP values in Group 2 were significantly lower during immersion than the control period ($P < 0.02$).

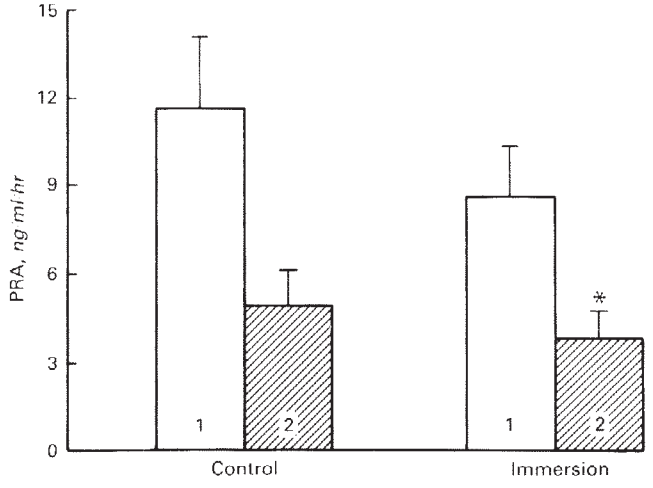

Fig. 4. *Plasma renin activity (PRA) is significantly higher in Group 1 than Group 2 patients, both with and without immersion.* The PRA in Group 2 were significantly lower during immersion than during the control period ($P < 0.05$).

± 1.2 ng/ml/hr, $P < 0.05$), and this difference was maintained during immersion (8.6 ± 1.7 vs. 3.8 ± 0.9 ng/ml/hr, $P < 0.05$) (Fig. 4). The suppression of renin with immersion reached statistical significance only in Group 2 patients ($P < 0.05$).

Plasma aldosterone was not significantly different in the two patient groups during the control studies, although plasma aldosterone concentrations tended to be higher in Group 1 (100 ± 21 vs. 75 ± 21 ng/dl, NS). During immersion, however, plasma aldosterone concentrations were higher in Group 1 versus Group 2 (82 ± 14 vs. 39 ± 10 ng/dl, $P < 0.05$) and only the values in Group 2 suppressed during the immersion procedure ($P < 0.02$).

Plasma norepinephrine concentrations were not significantly different in the two patient groups during the control studies (1168 ± 197 vs. 924 ± 203 ng/ml, NS). During immersion, however, plasma norepinephrine was significantly higher in Group 1 than Group 2 patients (1155 ± 183 vs. 603 ± 126 pg/ml, $P < 0.05$). Furthermore, only Group 2 patients exhibited a significant suppression of plasma norepinephrine during immersion ($P < 0.02$).

Discussion

In the present study, plasma hormone concentrations and renal hemodynamics were demonstrated to be significantly different in those non-excretor patients who excreted less than 40% of the water load during head–out water immersion (mean 21%) as compared to those who excreted greater than 40% of the water load during immersion (mean 67%). Although four patients of Group 2 increased their water excretion during immersion to 80% or greater, all of the 15 patients excreted less than 80% of the water load in the absence of immersion, that is, all were non-excretors.

The present results as well as previous studies [18–20] suggest that there may be continuum of impairment in water excretion in cirrhotic patients beyond that previously described [1]. In the earlier study [1], non-excretor patients (<80% of water load excreted over 5 hr) demonstrated hormonal indices of a decreased effective blood volume which were significantly increased compared to excretor patients (>80% of water load excreted over 5 hr). The present results extend these observations by further studying the characteristics of the non-excretor patients during head–out water immersion. In contrast to Group 2 patients, the Group 1 patients who excreted a mean of 14% before and 21% of the water load during immersion demonstrated higher concentrations of plasma vasopressin, renin, aldosterone, and norepinephrine, and failed to significantly suppress the plasma level of these hormones during head–out water immersion. These cirrhotic patients also were more hyponatremic; they demonstrated clinically tense ascites, and were diuretic–resistant. The Group 1 patients also demonstrated significantly lower clearances of inulin and para-aminohippurate in spite of comparable mean arterial pressures and cardiac indices. The increased renal vascular resistance and diminished renal hemodynamics were associated with higher plasma concentrations of renin, norepinephrine and vasopressin in the Group 1 patients. The decreased renal hemodynamics as well as the elevated concentrations of vasopressin and aldosterone were no doubt involved in the more profound impairment in renal excretion of sodium and water in the Group 1 as compared to the Group 2 patients.

Since mean blood pressures and cardiac indices were comparable in Groups 1 and 2, the explanation for the differences in renal hemodynamics and plasma hormone levels is intriguing. Since cardiac output was not lower in the Group 1 patients, caval compression secondary to their more tense ascites with a resultant decrease in venous return and cardiac output, did not account for the greater renal excretory impairment of the Group 1 patients [7, 8]. The present findings are compatible, however, with differences in the degree of diminished effective blood volume in the non-excretor cirrhotic patients in Group 1 and Group 2. In a recent study of cirrhotic patients from our laboratory, the level of peripheral vascular resistance was found to be a very important determinant of effective blood

volume [6]. In this regard, the present results are compatible with the concept of a greater initial peripheral vasodilation in the Group 1 patients during an earlier phase of their liver disease, and thus a more profound diminution in effective blood volume. In response to this greater circulatory inadequacy, increased sympathetic activity, activation of the renin–angiotensin system, and the nonosmotic release of vasopressin would be expected to occur. This sequence of events might then act to restore peripheral vascular resistance and blood pressure toward pre-cirrhotic levels, but at the same time lead to severe renal vasoconstriction and more avid retention of sodium and water [10, 11]. This interpretation is compatible with the higher plasma cocentrations of vasopressin, renin and norepinephrine and renal vascular resistance in the Group 1 patients, even though the systemic vascular resistances were comparable in the two groups. Similar increases in renal vascular resistance and sodium retention have been demonstrated in experimental arteriovenous fistulae [12]. In the steady–state condition, the cardiac index would be expected to be comparable in Groups 1 and 2, since the after load, as determined by peripheral vascular resistance, would be comparable in both groups. The present results are most compatible with this interpretation; however, patients with cirrhosis will need to be followed longitudinally in order to document definitively this proposed sequence of events.

Finally, there are several potential clinical implications arising from the present study. It would seem likely that the hyponatremic, diuretic–resistant cirrhotic patients with tense ascites (Group 1) are the most likely patients to progress to the state of hepatorenal syndrome. The much lower glomerular filtration rates and renal plasma flows in these Group 1 patients occurred in spite of comparable mean arterial pressures in both groups, indicating higher levels of renal vascular resistance in the Group 1 patients. Their higher and non-suppressible plasma levels of norepinephrine, renin and vasopressin are compatible with a role for the sympathetic nervous system, angiotensin, and vasopressin in mediating this higher level of renal vascular resistance. Thus, the patients in Group 1 might also be expected to experience a more profound lowering of blood pressure during alpha–adrenergic blockade [13], angiotensin antagonism [14, 21], and inhibition of the vascular effect of vasopressin (15). Furthermore, these diuretic resistant Group 1 patients may be potential candidates for peritoneovenous (LeVeen) shunting as a means to increase effective blood volume and improve renal excretory function [16]. In this regard, in a recent preliminary follow–up report on the present patients [22], Group 1 patients exhibited a significantly higher morbidity and mortality than the Group 2 patients. One patient in Group 1, however, received a LeVeen shunt and normalized his water excretion and was the only patient in this group to live longer than five months; he is still alive at 24 months. The Group 2 patients' survival is presently beyond an average of 28 months.

Acknowledgments

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